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Immunoregulation of Liver Fibrosis: New Opportunities for Antifibrotic Therapy

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Keywords

fibrogenesis, cirrhosis, regression of fibrosis, inflammation, immune cells, immunometabolism, autophagy, antifibrotic therapy

Abstract

Liver fibrosis develops in response to chronic liver injury and is characterized by a sustained inflammatory response that leads to excessive collagen deposition by myofibroblasts. The fibrogenic response is governed by the release of inflammatory mediators from innate, adaptive, and innate-like lymphoid cells and from nonprofessional immune cells (i.e., epithelial cells, hepatic myofibroblasts, and liver sinusoidal endothelial cells). Upon removal of the underlying cause, liver fibrosis can resolve via activation of specific immune cell subsets. Despite major advances in the understanding of fibrosis pathogenesis, there is still no approved antifibrotic therapy. This review summarizes our current knowledge of the immune cell landscape and the inflammatory mechanisms underlying liver fibrosis progression and regression. We discuss how reprogramming immune cell phenotype, in particular through targeting selective inflammatory pathways or modulating cell-intrinsic metabolism, may be translated into antifibrogenic therapies.

1. INTRODUCTION

MAFLD: metabolic dysfunction-associated fatty liver disease

HSC: hepatic stellate cell

LSEC: liver sinusoidal endothelial cell

MASH: metabolic dysfunction-associated steatohepatitis

CLD: chronic liver disease

Fibrosis is an exaggerated wound healing process, common across organs such as liver, lung, heart, and kidney, that develops as a consequence of chronic injury. It results from the accumulation of altered composition in the extracellular matrix due to an imbalance between increased synthesis and fibrolysis dysfunction (1). In the liver, the main causes of fibrosis are chronic viral infection, alcohol consumption, autoimmune diseases, or toxic diseases, but currently the main cause is metabolic dysfunction, often associated with diabetes, overweight, and hypertension, now called metabolic dysfunction-associated fatty liver disease (MAFLD). Whatever the origin, liver fibrosis can progress to end-stage cirrhosis, with a high morbidity-mortality risk due to severe complications, including hypertension, liver and organ failure, evolution to hepatic encephalopathy and coagulation disorders, and exposure to bacterial infections (2). In addition, cirrhosis, regardless of the etiology, is the strongest risk factor for hepatocellular carcinoma, with an overall annual incidence of 3%. Fibrogenesis is driven by myofibroblasts, originating mainly from hepatic stellate cells (HSCs) and portal fibroblasts (3, 4) that acquire fibrogenic, proliferative, immunomodulatory, contractile, and angiogenic properties in response to liver injury (1, 5). The triggering fibrogenic signal arises from damaged parenchymal cells (i.e., hepatocytes and cholangiocytes) through complex interactions with nonparenchymal cells, including immune cells and liver sinusoidal endothelial cells (LSECs), that lead to myofibroblast activation (6, 7). Fibrosis and even cirrhosis can regress, as described following successful antiviral therapy in patients with chronic viral hepatitis, immunosuppression in autoimmune hepatitis, or lifestyle modifications and bariatric surgery in patients with metabolic dysfunction-associated steatohepatitis (MASH) (8–10). However, these approaches are not always possible or available and the development of antifibrotic strategies is still urgently needed.

Dysregulated inflammation is a characteristic feature of chronic liver diseases (CLDs), and changes in immune cell phenotype not only determine CLD progression to fibrosis/cirrhosis and the occurrence of complications but also govern CLD regression via distinct immune cell subsets (11, 12). The inflammatory response results from the hepatic release of inflammatory mediators by professional immune cells (i.e., innate, adaptive, and innate-like lymphoid cells) and nonprofessional immune cells (i.e., epithelial cells, hepatic myofibroblasts, and LSECs) that perpetuate fibrogenesis.

In addition to intrahepatic signals, extrahepatic sources of inflammatory mediators, in particular those originating from the gut and/or the adipose tissue, contribute to fibrosis development. The gut–liver cross talk illustrates the importance of extrahepatic factors in liver fibrosis (13). Indeed, disruption of the gut barrier and dysbiosis are characteristic features of CLDs, resulting in the release of bacterial products that flow to the liver and promote activation and recruitment of immune cells, in particular through activation of pattern recognition receptors such as Toll-like receptor 4. Dysbiosis also modifies bile acid composition, which in turn alters the gut microbiome (13). Proinflammatory signals originating from adipose tissue are described mainly in the context of MAFLD, where the dysregulation of adipokine secretion (i.e., increase in leptin and decrease in adiponectin) promotes inflammation, insulin resistance, and release of free fatty acids and proinflammatory cytokines that participate in lipotoxic hepatocyte death, hepatic inflammation, and fibrosis (14, 15).

Unraveling the complex interplay between these inflammatory pathways and fibrogenesis should help researchers develop effective strategies to improve patient outcome. In this review, we describe the immune cell landscape and the inflammatory mechanisms underlying liver fibrosis progression and regression and discuss the antifibrogenic potential of therapeutic interventions targeting selective inflammatory pathways or specific immune cells.

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2. THE IMMUNE CELL LANDSCAPE DURING LIVER FIBROSIS PROGRESSION

2.1. Professional Immune Cells

Initially, studies were restricted to the involvement of macrophages and conventional T cells and the description of the profibrogenic properties of selected cytokines and chemokines. Single-cell and spatial transcriptomics studies of human samples and experimental models have complexified the fibrogenic picture with the description of distinct immune cell subsets' diversity reflecting their plasticity, associated with a progressive change in their frequency, localization, and functions with disease progression (16, 17).

SAM: scar-associated macrophage

CCR: C-C chemokine receptor

LAM: lipid-associated macrophage

DC: dendritic cell

2.1.1. Innate immune cells. Among immune cells, macrophages are major contributors of liver fibrogenesis, as initially revealed by global genetic and chemical depletion of macrophages in experimental models of chronic liver injury that uncovered their dual profibrogenic and antifibrogenic functions in fibrosis progression and regression, respectively (18) (**Figure 1**). Macrophages consist of a heterogeneous population even in a healthy liver, where they harbor a wide spectrum of expression profiles (19–22). They comprise resident Kupffer cells, which derive from erythromyeloid progenitors (23), and infiltrating monocyte-derived macrophages, which originate preferentially from the bone marrow but also from the peritoneal cavity or the spleen (21, 24). Activated Kupffer cells and recruited monocyte-derived macrophages produce TGF-β1, the main fibrogenic cytokine, but also proinflammatory cytokines and chemokines, including TNF, IL-1β, CCL2, or CCL5, that drive HSC activation and the recruitment of other inflammatory cells (6).

The current scheme is that the resident TIM4^{+} Kupffer cell pool is depleted and dedifferentiated during chronic liver injury (21, 25–29). The Kupffer cell pool is replenished with monocyte-derived Kupffer cells that display a more inflammatory phenotype and the capacity to form Kupffer cell–like syncytia that retain antibacterial properties (21, 27, 30). These infiltrating monocytes also differentiate into scar-associated macrophages (SAMs), which stimulate collagen production by HSCs in coculture and accumulate in portal fields and close to (proliferating) bile ducts in patients with cirrhosis from different etiologies (25, 31). Mouse liver SAMs, with high expression of Ly6C (Ly6C^{hi}) and C-C chemokine receptor 2 (CCR2), were initially described. SAMs in mouse and human samples from patients with cirrhosis were further characterized by their expression of *CD9*, *TREM2*, and *SPP1* (31, 32) and by the coexpression of *GPNMB*, *CD63*, and *FABP5* (33). Their differentiation from monocytes is driven by type 3 cytokines, including IL-17 and granulocyte-macrophage colony-stimulating factor (33). Because fibrosis shares common mechanisms across organs, SAMs were also identified in the lung of patients with idiopathic pulmonary fibrosis and in mouse models of lung fibrosis, suggesting that this macrophage population may have broader profibrotic functions across organs and species (33). However, SAMs share phenotypic similarities with lipid-associated macrophages (LAMs), a subpopulation that displays protective properties against metabolic dysregulation in the liver (20, 34–37); in addition, recent data demonstrate that TREM2, a phenotypic marker of SAM and LAM, displays antifibrogenic properties (38). Therefore, further phenotypic characterization allowing for distinction between SAM and LAM profiles and functions is still required.

Besides macrophages, alterations of other innate immune cell populations, including dendritic cells (DCs), neutrophils, and mast cells (**Figure 1**), in experimental models of chronic liver injury and patients with CLD have been described, but their role in fibrogenesis remains to be further clarified. Depletion of DCs leads to reduced hepatic inflammation and fibrosis (39). DCs enhance liver inflammation through interactions with T cells and natural killer (NK) cells and increase the inflammatory and proliferative properties of HSCs (39). However, their profibrogenic role has

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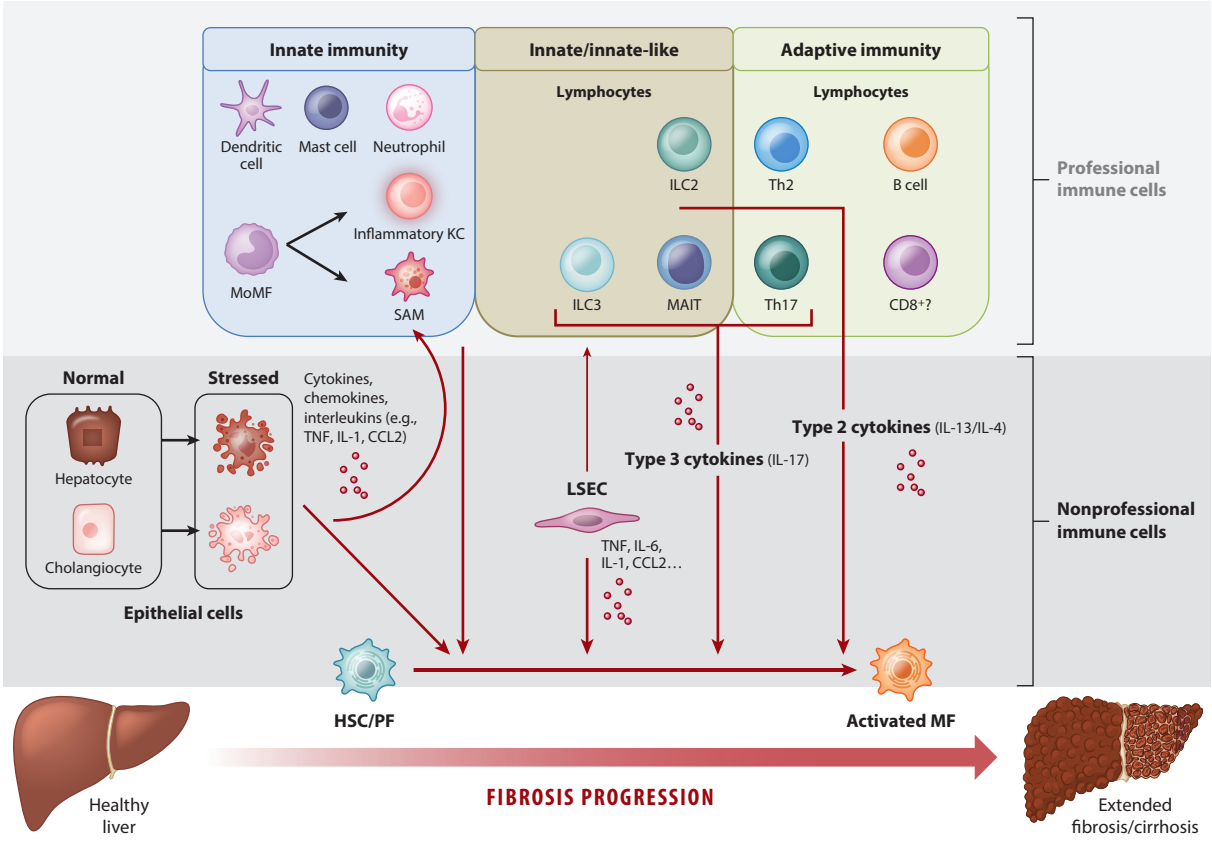

Figure 1

Immune cells and inflammatory pathways involved in fibrosis progression. Nonprofessional immune cells such as injured epithelial cells (hepatocytes and cholangiocytes) and LSECs, as well as professional immune cells from innate, innate-like, and adaptive immunity, release cytokines that participate in the activation of fibrogenic cells, namely HSCs and PFs, into MFs. Within the innate immune cell compartment, inflammatory KCs and SAMs are major regulators of fibrosis progression. Within the adaptive and innate lymphoid cell compartment, type 2 (ILC2 and Th2 lymphocytes) and type 3 (ILC3, MAIT, and Th17) cytokine-producing cells play a central role. Abbreviations: HSC, hepatic stellate cell; ILC, innate lymphoid cell; KC, Kupffer cell; LSEC, liver sinusoidal endothelial cell; MAIT, mucosal-associated invariant T; MF, myofibroblast; MoMF, monocyte-derived macrophage; PF, portal fibroblast; SAM, scar-associated macrophage.

been challenged (40) and a role for DCs in fibrosis resolution was also reported (41), suggesting the existence of specific DC subsets with opposite functions during fibrogenesis. An additional X-C motif chemokine receptor 1 ($XCR1^+$) classical DC1 subset has recently been identified that promotes inflammatory T cell reprogramming and worsens MASH features, but direct interactions with HSC fibrogenic properties remain to be demonstrated (42). Neutrophil recruitment is also a common feature in patients and mice with CLD. Neutrophils contribute to liver inflammation by generating reactive oxygen species and proinflammatory mediators, leading to hepatocyte death and HSC activation (43, 44). However, they show impaired phagocytic function in patients with advanced liver diseases, and their contribution to fibrosis resolution suggests the existence of distinct subsets with proinflammatory and restorative functions (45). Finally, mast cells, traditionally described for their involvement in allergic responses and immune regulation, show fibrogenic properties in experimental models of chronic liver injury (46, 47).

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2.1.2. Conventional and nonconventional lymphocytes. Conventional T and B lymphocytes, the main effectors of adaptive immunity, reside around portal veins in the quiescent liver and are also recruited into the parenchyma during CLD (12, 48–50). This infiltrate is correlated with the extent of fibrosis in patients with MASH (12, 48). Conventional and nonconventional T cells are important components of the antimicrobial response but are also drivers of the inflammatory and fibrogenic response, depending on the subsets and activation status (12, 50, 51).

ILC: innate lymphoid cell

iNKT: invariant natural killer T

MAIT: mucosal-associated invariant T

2.1.2.1. B lymphocytes. B lymphocytes with an activated profile accumulate in the liver during chronic liver injury, as described for patients with cirrhosis and murine models of fibrosis. Their profibrogenic properties were initially demonstrated in B cell–deficient mice, which are partly protected in toxic- or regimen-induced models of fibrosis (52–55). The additional contribution of B cells from the intestine to fibrogenesis was also recently demonstrated via immunoglobulin A secretion and binding to Fcγ receptors, leading to activation of hepatic myeloid cells (56). However, a dual role of B cells was also revealed, with the characterization of an IL-10 antifibrogenic B cell subset in a mouse model of MASH (54) (**Figure 1**).

2.1.2.2. T lymphocytes. Historically, studies have focused on the role of conventional $CD4^+$ T cells, describing an overproduction of Th2 (IL-4/IL-13) cytokines during fibrosis progression and a reduction of Th1 (IFN-γ) antifibrogenic signaling (57). Further, a strain-specific susceptibility to fibrosis in mice was reported. Depending on the Th1/Th2 balance, BALB/c mice showed a predominant Th2 response and severe fibrosis, while C57BL/6 mice displayed a Th1 response associated with minimal fibrosis (58). This traditional view was challenged by the characterization of additional new conventional and nonconventional T cell players, including the Th17 (IL-17/IL-22 producing) $CD4^+$ subset, and the identification of hepatic innate lymphocytes that comprise innate-like T cells and innate lymphoid cells (ILCs) (12, 50). Innate-like T cells are abundant in the liver, where they represent the main source of liver T lymphocytes, including γδ T cells, invariant natural killer T (iNKT) cells, and mucosal-associated invariant T (MAIT) cells (51). ILCs comprise cytotoxic NK cells and ILC1, ILC2, and ILC3 subsets. Since they also produce IFN-γ, IL-4/IL-13, and IL-17, a broader classification (type 1, 2, and 3) has been proposed on the basis of cytokine production. Type 1 immunity is characterized mainly by production of IFN-γ and is mediated by $CD4^+$ Th1 cells, $CD8^+$ cytotoxic T cells (Tc1), ILC1 cells, and NK cells, as well as MAIT cell (MAIT1) and γδ T subsets. Type 2 immunity is defined by the production of IL-4, IL-5, and IL-13 and is mediated by $CD4^+$ Th2 cells, $CD8^+$ (Tc2) cells, and ILC2 cells. Type 3 immunity is characterized by the production of the Th17-associated cytokines IL-17A to F IL-21, and IL-22 and is mediated by $CD4^+$ Th17 cells, $CD8^+$ Tc17 cells, ILC3 cells, MAIT cells, iNKT cells, and γδ T cells. Whereas type 2 and 3 cytokines are profibrogenic, type 1 immunity is considered antifibrogenic (**Figure 1**) and is described in Section 3.2.

Increased levels of type 2 cytokines, in particular IL-13 and the Th2/ILC2 stimulus IL-33, are observed in patients with CLD of several etiologies (viral, autoimmune, or metabolic) (59, 60). The profibrogenic properties of IL-13 have been characterized mainly in parasitic liver diseases induced by schistosomiasis infection (61, 62), and confirmed in a mouse model of MAFLD (63). Cell culture experiments further demonstrated that IL-13 directly activates HSCs, thereby increasing collagen deposition in the liver, and shifts macrophages toward a TGF-β-producing phenotype (59, 64). Mechanistically, data from human samples and mouse models suggested that ILC2 is likely to constitute a major source of IL-13, and its contribution to fibrogenesis was demonstrated by adoptive transfer of ILC2 in IL-13-deficient mice that resulted in exacerbated fibrosis (59, 65). Additional fibrogenic contribution of type 2 cytokines released by NKT cells and by a nonconventional ILC3 subset has also been evoked (66, 67).

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Type 3 cytokines, comprising IL-17 and IL-22, are a signature of advanced liver fibrosis in human and animal liver samples. Whereas IL-22 displays hepatoprotective and proregenerative properties (68, 69), controversial data on its pro- or antifibrogenic role have been reported (70–72). In contrast, profibrogenic properties of IL-17 are well characterized. Indeed, mice deficient in either IL-17 or IL-17R show resistance to fibrosis upon chronic liver challenge. Further, the number of IL-17-expressing T cells is increased in the fibrotic scar (71–77). Mechanistically, activation of IL-17 receptors expressed by hepatocytes, HSCs, and macrophages results in inflammatory and fibrogenic responses (71, 74, 77–79). The main sources of IL-17 are $CD4^+$ Th17, MAIT cells, γδ T cells, and ILC3, which display an activated profile in patients with and experimental models of chronic liver injury and have all been associated with the development of fibrosis. Among them, MAIT cells are considered the predominant source of IL-17, as they represent 20–40% of resident T cells in human livers, and MAIT cell ligands are abundant in the peripheral blood during CLD (51, 73, 80, 81). In patients with severe fibrosis, MAIT cells accumulate in the fibrotic septa and display a predominant $IL\text{-}17^+$ (MAIT17) phenotype. However, they are rare in mice, and the use of animals enriched in MAIT cells has been useful to study their impact on liver fibrosis. Mice models deficient or enriched in MAIT cells demonstrated proinflammatory and profibrogenic properties via T cell receptor–mediated profibrogenic and proinflammatory effects on hepatic myofibroblasts and cytokine-dependent proinflammatory effects on hepatic macrophages (73, 81).

NKT cells are a heterogeneous resident population of T cells (type I or iNKT and type II), with type I being more abundant in the mouse liver than in the human liver. The frequency of hepatic iNKT cells correlates with the severity of hepatic inflammation and advanced fibrosis in patients with MAFLD (12). According to their capacity to produce type 1, 2, and 3 cytokines, NKT cell subsets display profibrogenic and antifibrogenic properties in mouse models related to the production of IL-4, IL-13, and IL-17, on the one hand, and to IFN-γ-mediated HSC death, on the other hand (66).

Among other conventional T cell subsets, direct demonstration of the impact of $CD8^+$ T cells on fibrosis progression is lacking, although recent studies have identified an autoaggressive $CXCR6^+CD8^+$ T cell population in human and murine MASH with deleterious effects on liver damage (82). However, whether this $CD8^+$ T cell subset directly regulates HSC functions and fibrogenesis remains to be evaluated. The role of regulatory T cells (Tregs) in fibrogenesis is unclear because of their immunosuppressive properties, their capacity to protect HSCs from NK cell death, and their inhibitory IL-10-mediated effect on HSCs (83). However, in the context of MASH-induced liver fibrosis, Tregs produce the EGFR ligand amphiregulin, thereby promoting metabolic liver fibrosis through direct interaction with HSCs (84).

2.2. Nonprofessional Hepatic Immune Cells Also Drive the Inflammatory-Mediated Fibrogenic Response

Besides professional immune cells, liver epithelial cells, LSECs, and HSCs display innate and adaptive features, including the capacity to secrete inflammatory mediators, phagocytose dead cell debris, and present antigens. In this context, their contribution to the immunoregulation of liver fibrosis is now well admitted.

2.2.1. Liver epithelial cells. Death of hepatocytes (in the context of alcoholic, metabolic, or viral diseases) or cholangiocytes (in the context of autoimmune diseases) is a cardinal feature and an initiating event of CLD progression to fibrosis. Damaged epithelial cells produce a large variety of inflammatory mediators that contribute to fibrosis progression through direct or indirect cross talk with HSCs (**Figure 1**). Direct activation of HSCs is driven by the release of damage-associated molecular patterns by dying hepatocytes, such as UDP-glucose and UDP-galactose, or

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secretion of NLRP3 inflammasome particles (85). Indirect activation of HSCs is also promoted by inflammatory mediators produced by stressed hepatocytes, including IL-11, IL-33, CCL2, CXCL1, CXCL2, SPP1, cysteine-rich angiogenic inducer 61 (CYR61), and natural killer group 2 member D ligand (NKG2D-L), that recruit or activate monocyte-derived macrophages, ILCs (ILC2), or γδ T cells (59, 77, 86–89). Similarly, in the context of biliary diseases, damaged cholangiocytes secrete inflammatory mediators with profibrogenic properties, including CCL2, TNF, and IL-1, that will directly interact with HSCs or amplify the inflammatory reaction (90, 91).

Besides releasing inflammatory mediators, hepatocytes and cholangiocytes can behave as antigen-presenting cells through T cell receptor–dependent interactions with conventional $CD4^+$ and $CD8^+$ T cells or nonconventional T lymphocytes such as MAIT and NKT cells with proinflammatory and profibrogenic properties (80, 90, 92).

2.2.2. Hepatic myofibroblasts. Activation of HSCs during chronic liver injury is promoted by various components of the inflammatory microenvironment, since HSCs express multiple pattern recognition receptors, chemokine and cytokine receptors, and the inflammatory signaling machinery (6). But interactions between HSCs and immune cells are bidirectional; besides their matrix-producing and proliferative functions, activated HSCs contribute to the inflammatory reaction by secreting chemokines (e.g., CCL2, CCL5, CXCL9), cytokines (e.g., IL-8, TNF, IL-6), and leukocyte adhesion molecules [intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], all of which attract immune cells and amplify the inflammatory response (5) (**Figure 1**). In addition, HSCs display features of antigen-presenting cells, since they express MHC class I and II molecules and MR1, allowing presentation to $CD4^+$ or MAIT cells (80). They are also characterized by phagocytic properties, which underlie activation of their fibrogenic properties. In keeping with their innate and adaptive properties, single-cell RNA-sequencing studies have revealed that HSCs are a heterogeneous population of cells and confirmed the existence of subsets bearing an inflammatory phenotype (31, 93–96).

2.2.3. Liver sinusoidal endothelial cells. LSECs are gatekeepers that prevent HSC activation in the normal liver and display immunomodulatory properties, with the capacity to maintain tolerance. In response to chronic injury, LSECs lose their differentiated phenotype (a process termed capillarization) and their capacity to suppress HSC activation (97). They also become highly proinflammatory and secrete a series of cytokines, chemokines, and adhesion molecules (TNF-α, IL-6, IL-1, CCL2, ICAM-1, VCAM-1) that underlie their profibrogenic properties through interaction with HSCs or macrophages. Finally, LSECs gain enhanced capacity to capture and present antigens (97). Furthermore, single-cell RNA sequencing of liver from patients with cirrhosis led to the identification of an endothelial cell subpopulation characterized by the expression of atypical chemokine receptor 1 (*ACKR1*), a gene that regulates leukocyte recruitment (31).

3. LIVER FIBROSIS REGRESSION IS DRIVEN BY SPECIFIC RESTORATIVE IMMUNE CELL SUBSETS

Mechanistic studies of fibrosis regression are obviously restricted to animal models. They rely on the removal of the injured agents in mice with established fibrosis, most commonly cessation of toxic (i.e., CCl_4) or metabolic (i.e., choline-deficient L-amino acid–defined high-fat diet) injuries. In these models, extracellular matrix degradation, characterized by a shift in the balance toward fibrolysis at the expense of matrix synthesis, is associated with reversion of the HSC phenotype to a quiescent state and/or clearance of activated or senescent HSCs by apoptosis (98, 99). However, the respective contribution of these mechanisms to fibrosis regression is still unclear. Although reversion of HSCs to a quiescent-like phenotype is associated with matrix degradation, these cells remain more sensitive to an additional fibrogenic challenge (98, 99), but the role of immune cells

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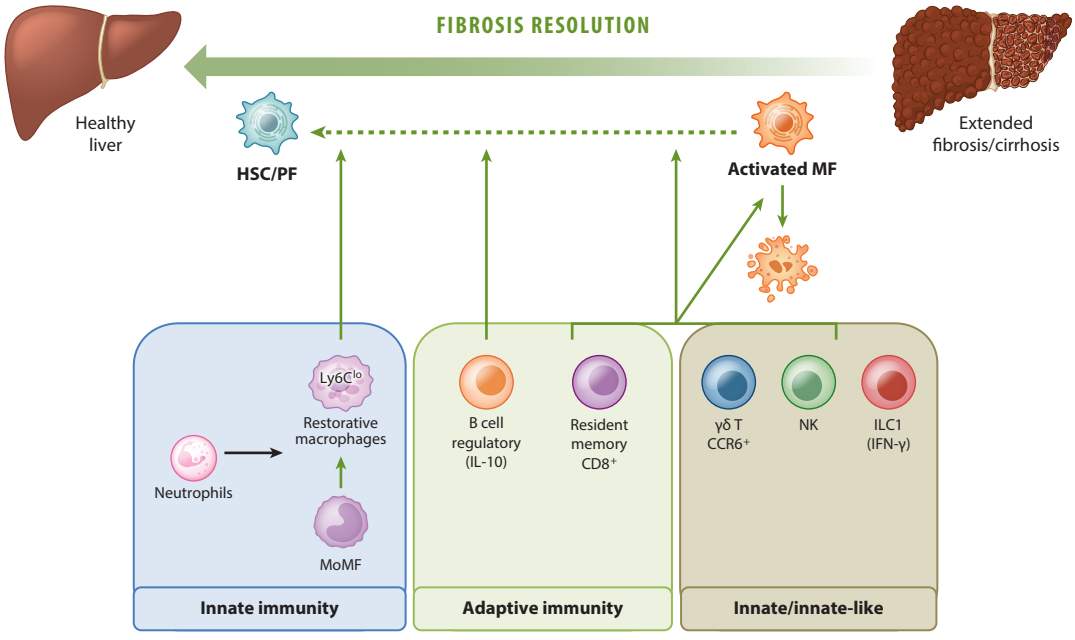

Figure 2

Immune cells involved in fibrosis regression. Activated hepatic MFs can revert to a quiescent-like phenotype or apoptosis induced by various immune cell subsets, including $CD8^+$ T cells with a resident memory phenotype, $CCR6^+$–γδ T cells, and NK cells. A subset of B cells expressing IL-10 has also been described as antifibrogenic. $Ly6C^{lo}$ macrophages with restorative functions (i.e., higher phagocytic properties, higher matrix-degrading capacity, anti-inflammatory properties) play a major role in fibrosis resolution. Their phenotype is controlled by other immune cells, such as neutrophils. Abbreviations: CCR6, C-C chemokine receptor 6; HSC, hepatic stellate cell; ILC, innate lymphoid cell; MF, myofibroblast; MoMF, monocyte-derived macrophage; NK, natural killer; PF, portal fibroblast.

in this process has not been characterized. In contrast, the role of hepatic ILC subsets in HSC clearance has been highlighted, in particular that of NK cells, γδ T cells, and tissue resident $CD8^+$ T cells (100–105). However, for efficient resolution of fibrosis, digestion of extracellular matrix is also required and is driven by a subpopulation of restorative macrophages.

3.1. Innate Lymphoid Cells and Clearance of Hepatic Stellate Cells

Several ILC subsets promote HSC clearance (**Figure 2**). In particular, NK cells induce HSC apoptosis through several mechanisms: (*a*) via NK receptor NKG2D interacting with its ligand, retinoic acid early inducible 1 (RAE-1), expressed on HSCs; (*b*) via tumor necrosis factor–related apoptosis-inducing ligand (TRAIL)-mediated killing; (*c*) by producing FasL, which interacts with Fas expressed by HSCs; and (*d*) by shifting toward an ILC1-like IFN-γ-producing phenotype, leading to decreased HSC activation and reduced fibrosis (100–103, 106). The antifibrogenic effects of NK cells and IFN-γ are suppressed at advanced stages of chronic liver injury and may contribute to fibrosis progression (101). However, since IFN-γ can also be produced by ILC1, the contribution of ILC subsets to the antifibrogenic properties of IFN-γ also needs to be further explored.

Both hepatic γδ T cells and a subset of $CD8^+$ T cells with a resident memory phenotype display apoptotic properties toward HSCs through a Fas/FasL pathway and promote fibrosis resolution (104, 105). Although hepatic γδ T cells promote IL-17 release in mouse models of liver fibrosis, and therefore indicate a profibrogenic function (76, 77), the antifibrogenic properties

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of a CCR6-expressing γδ T cell subset have also been described (104). These antifibrogenic effects are mediated through the induction of HSC apoptosis in a FasL-dependent manner, the enhancement of NK cell–mediated cytotoxicity via the release of IFN-γ, or both (104, 107).

3.2. Innate Immune Cells and Fibrosis Resolution

Among immune cells contributing to fibrosis resolution, a subset of restorative macrophages has been the most studied (18, 108); although the existence of a restorative DC subset was suggested, further evaluation is needed (41). The role of macrophages in fibrosis resolution was initially identified in mice with established liver fibrosis, in which failure to degrade extracellular matrix was observed when macrophages were depleted upon cessation of injury. Restorative macrophages were further characterized by their low expression of Ly6C (Ly6C^{lo}) (108). They also express the macrophage scavenger receptor stabilin-1 (109) and chemokine receptors with antifibrogenic and anti-inflammatory properties such as CX3CR1, and they display high phagocytic and efferocytic properties that may contribute to resolve injury and fibrosis (108, 110). In addition, they show high matrix-degrading capacities and high expression of matrix metalloproteinases (MMP12 and MMP13) (108). Their origin is still not established, but they most likely result from a phenotypic switch of proinflammatory/profibrogenic macrophages, although the existence of a separate subset cannot be excluded.

The switch from profibrogenic macrophages to restorative macrophages is controlled by other immune cell populations, in particular neutrophils and MAIT cells. Indeed, mice with established CCl_4- or diet-induced liver fibrosis show impaired spontaneous resolution of inflammation and fibrosis when neutrophils are depleted (45, 111). Failure to resolve is consecutive to the blockade of macrophage switch from profibrogenic to restorative phenotype (45). In addition to their role in fibrosis progression, MAIT cells block fibrosis resolution by impairing restorative macrophage emergence. When MAIT cell activation is blocked by acetyl-6-formylpterin, fibrosis regression is accelerated, both in animal models and in precision-cut liver slices from patients with cirrhosis, via an increase in restorative macrophages at the expense of SAMs with apoptotic features (112). These data are in line with the description of anti-inflammatory macrophages that can trigger apoptosis of proinflammatory macrophages via the production of IL-10, leading to protection against the early stages of chronic liver injury (113).

4. INFLAMMATION AS A GRAIL FOR ANTIFIBROGENIC THERAPY?

Although major advances in our understanding of fibrogenesis have been made, with efficacy of antifibrogenic treatments demonstrated in preclinical models, the results of clinical trials have been disappointing so far. In this context, targeting the resolution of inflammation is considered an attractive option. Monocytes and macrophages are the immune cell types most commonly considered for targeting. However, broader approaches are being evaluated, including either inhibition of the production of inflammatory mediators or inflammatory pathways, whatever their cellular origin, or modulation of cell-intrinsic metabolic pathways that may not only affect immune cell phenotype but also limit hepatocyte damage, HSC activation, or endothelial dysfunction. Currently, promising antifibrogenic drugs have been tested only in patients with MASH (114, 115) (**Figure 3**).

4.1. Macrophage-Based Cell Therapy

The efficacy of a macrophage-based therapy has been demonstrated in mouse models by the reduction of liver fibrosis attained following infusion of differentiated macrophages (116, 117). Mechanistic studies demonstrated that the antifibrogenic effect relies on both HSC-induced

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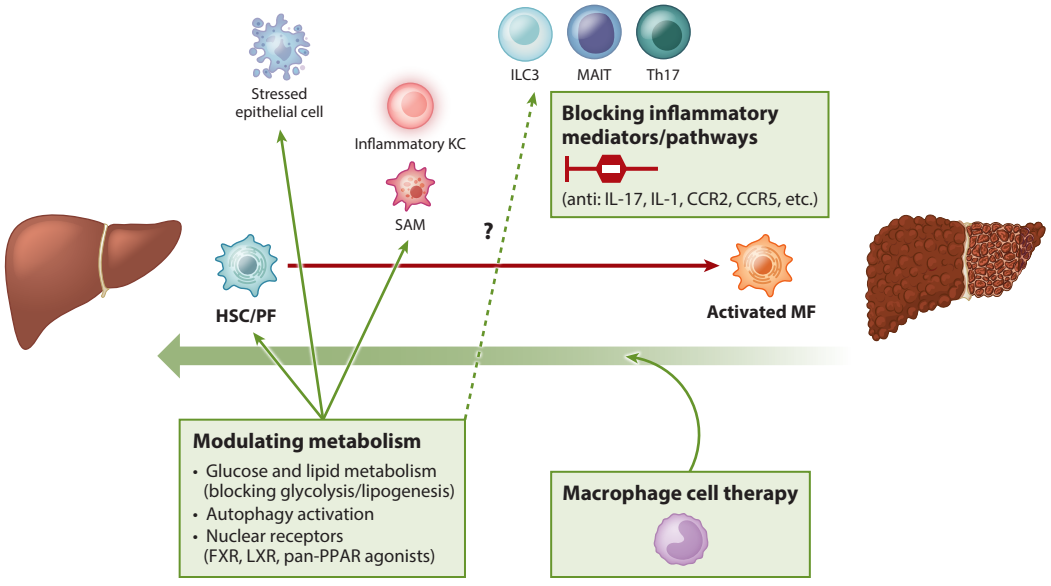

Figure 3

Immunoregulation of liver fibrosis: therapeutic approaches. Current strategies that target immune cells include infusing macrophages that express markers of tissue repair; targeting selective inflammatory mediators/pathways, such as pharmacological antagonism of chemokine receptors or neutralization of chemokines, type 3 cytokines, or IL-1 signaling pathways; and modulating immune cell metabolism through the inhibition of glycolysis or lipogenesis, the activation of autophagy, or the induction of nuclear receptors. Modulating metabolism may additionally affect different cell types (i.e., restrain HSC activation and protect against epithelial cell injury). Abbreviations: CCR, C-C chemokine receptor type; FXR, farnesoid X receptor; HSC, hepatic stellate cell; ILC, innate lymphoid cell; KC, Kupffer cell; LXR, liver X receptor; MAIT, mucosal-associated invariant T; MF, myofibroblast; NK, natural killer; PF, portal fibroblast; PPAR, peroxisome proliferator-activated receptor; SAM, scar-associated macrophage.

apoptosis by NK cells and the recruitment of Ly6C^{lo} macrophages (116). The feasibility of the approach was further demonstrated by a Phase I clinical trial that injected autologous macrophages that express markers of tissue repair and inflammation resolution and showed an improvement in liver function and reduction of fibrosis markers (118). A Phase II study to further evaluate the efficacy of this approach is still ongoing (119).

4.2. Therapies Targeting Inflammatory Mediators or Inflammatory Pathways

Neutralization of cytokines/chemokines, by antagonizing their receptors or their signaling pathways, is anticipated to blunt the recruitment of proinflammatory monocytes/macrophages and limit HSC activation (120). Pharmacological inhibition of CCL2 by mNOX-E36 (121) or the use of cenicriviroc, a CCR2/CCR5 antagonist, gave promising anti-inflammatory and antifibrogenic results in mouse models (122). However, translational studies were disappointing. Although cenicriviroc showed antifibrotic efficacy in a Phase IIb clinical trial, these data were not confirmed in a larger Phase III trial (123, 124), but the compound is still considered for combined therapies. Blocking type 3 cytokines, in particular neutralizing IL-17, could constitute an interesting strategy, since the use of monoclonal IL-17 antibodies in the context of autoimmune diseases is already under evaluation (125). Despite the contribution of type 2 cytokines to fibrogenesis, their neutralization has not been considered because of their potential immunosuppressive consequences, the high risk of infection in patients with cirrhosis, and their potential onco-promoting properties. Finally, neutralization of IL-1β or blockade of its receptor or of the NLRP3 inflammasome signaling pathway could be considered an appropriate approach,

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especially since the IL-1β receptor antagonist anakinra is currently being evaluated to limit inflammation in patients with alcoholic hepatitis (126, 127).

Among the growth factor families, targeting fibroblast growth factors (FGFs) has recently gained attention with the description of the profibrogenic properties of FGF12 in myeloid cells and the beneficial consequences of its blockade through the decrease in the frequency of profibrogenic Ly6C^{hi} macrophages and of the expression of proinflammatory cytokines (128). Anti-inflammatory (e.g., FGF1, FGF2, FGF5, FGF21) or proinflammatory (e.g., FGF7, FGF10) fibrogenic effects of additional members of this large family have also been described, therefore opening potential new therapeutic perspectives (129).

FGF: fibroblast growth factor

PKM2: pyruvate kinase muscle isozyme 2

PFKFB3: 6-phosphofructo-2-kinase/fructose-2,6-biphosphate 3

4.3. Modulating Cell-Intrinsic Metabolism: Immunometabolism and Beyond

Metabolic reprogramming of immune cell phenotypes (immunometabolism) is critical to support their energy and anabolic demands and is directly linked to acquisition and/or changes in their phenotype and effector functions. The essential role of immune cell metabolic reprogramming in the orchestration of the wound healing response, particularly in fibrosis progression or regression, has only recently emerged (130–132). Obviously, changes in metabolism are not restricted to immune cells. Parenchymal and other nonparenchymal cell metabolism also participates in the wound healing response, suggesting that simultaneously targeting common metabolic pathways in different cell types could be achieved and useful for antifibrotic therapy. Up to now, clinical trials with the aim to modulate metabolism as an antifibrogenic strategy have been achieved mostly in the context of metabolic liver diseases (i.e., in patients with MASH).

4.3.1. Autophagy. Autophagy not only is a master cell metabolic regulator but also controls immune cell phenotype. In particular, activation of a noncanonical form of autophagy (LC3-associated phagocytosis) shifts the macrophage phenotype toward an anti-inflammatory stage with resulting antifibrogenic effects (133, 134). More generally, activating autophagy may be considered an interesting antifibrogenic approach: Besides its anti-inflammatory effects, activation of autophagy protects against hepatocyte injury, improves endothelial dysfunction, and decreases the release of profibrogenic extracellular vesicles from HSCs (133, 135–138). Loss-of-function mutations of the autophagic gene *ATG7* increase the risk of developing severe MAFLD and predispose individuals to cirrhosis and hepatocellular carcinoma (139). As a proof of concept, activation of autophagy reduces liver fibrosis in experimental models, but antifibrogenic effects remain to be validated with selective molecules in clinical trials (140–143).

4.3.2. Glucose and lipid metabolism. Glycolysis is fundamental for the functions of innate immune cells, including inflammatory macrophages, DCs, and neutrophils, but also for that of innate-like and adaptive immune cells, in particular to adopt an IL-17^{+} phenotype. In the context of liver fibrosis, activation of pyruvate kinase muscle isozyme 2 (PKM2) increases glycolysis, leading to macrophage reprogramming toward a profibrogenic phenotype in mouse models (131, 144). More generally, inhibiting glycolysis, with 2-deoxyglucose or pharmacological inhibitors of hexokinase 6-phosphofructo-2-kinase/fructose-2,6-biphosphate 3 (PFKFB3) or PKM2, has a global beneficial impact on liver fibrosis in mouse models, which includes not only reduced inflammation but also blockade of HSC activation and attenuation of endothelial dysfunction (131, 132). However, even if some drugs improved the histological features of MASH such as lobular inflammation, larger trials with fibrosis as an end point are still needed to conclude on the efficacy of glucagon-like peptide 1 receptor (GLP1R) agonists (liraglutide, semaglutide), sodium glucose transporter 1/2 inhibitors (e.g., dapagliflozin), or hexokinase inhibitors (145).

Although lipogenesis is anticipated to display inflammatory effects in macrophages and to shift T lymphocytes toward a Th17 phenotype, data in the context of liver fibrosis are lacking.

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LXR: liver X receptor

FXR: farnesoid X receptor

PPAR: peroxisome proliferator-activated receptor

However, lipogenesis is profibrogenic in animal models, resulting from the accumulation of lipotoxic lipids in hepatocytes and the activation of HSCs (146). Moreover, blockade of stearoyl-CoA desaturase-1 (aramchol), acetyl-CoA carboxylase (ACC) (firsocostat), or fatty acid synthase (denifanstat) has antifibrogenic effects in mouse models (147–149), but either it gave disappointing results in monotherapy clinical trials or Phase III results are still pending (150). Manipulation of lipid metabolism with resulting anti-inflammatory and antifibrogenic effects can also be achieved through limiting accumulation of free cholesterol (151) or inhibiting the arachidonic acid pathway by targeting monoacyl glycerol lipase (152).

4.3.3. Nuclear receptors. Liver macrophages, HSCs, and hepatocytes express various nuclear receptors that are at the crossroads of metabolism and inflammation. Liver X receptors (LXRs) are expressed in all liver cell types (hepatocytes, Kupffer cells, endothelial cells, and HSCs). LXR activation has antifibrogenic properties by limiting macrophage release of inflammatory cytokines but also by acting on HSC activation and endothelial cell capillarization. Since LXR agonists stimulate de novo lipogenesis, inverse agonists have been developed and have showed antifibrogenic effects in mouse models of MASH and alcoholic steatohepatitis (153–155). Farnesoid X receptors (FXRs) are expressed mainly in hepatocytes, but FXR agonists also display antifibrotic and anti-inflammatory effects in experimental mouse models and clinical trials. Further, results from the REGENERATE Phase III clinical trial of the FXR agonist obeticholic acid confirmed the improvement in liver fibrosis score (156). Finally, peroxisome proliferator-activated receptors (PPARs) are differentially expressed in liver cells, with PPARα present mostly in hepatocytes while PPARγ is expressed by macrophages and HSCs. The pan-PPAR agonist, lanifibranor, has shown antifibrotic efficacy in a Phase IIb study, further supporting a Phase III clinical trial (157). A major step forward in the field has been the demonstration of the efficacy of resmetirom, a thyroid hormone receptor β agonist recently approved by the US Food and Drug Administration that reduces fibrosis in patients with MASH (115).

In conclusion, the multi-omics revolution has repositioned inflammation and the diversity of immune cell subsets at the center of fibrogenesis. Better understanding of how their spatial distribution affects their phenotype is now required to better translate new concepts into immune-targeted antifibrogenic therapies. Because of immune cell plasticity, another challenge is to define the optimal timeframe for therapeutic intervention. Antifibrotic strategies are still in their infancy, in particular because the transition from experiments using mouse models to clinical trials has often proven disappointing. The current, most promising approaches are to combine therapies with molecules that target multiple pathways, such as metabolism and inflammation. Along these lines, combinations of FXR agonists and ACC or CCR2/CCR5 inhibitors, or approaches that combine three molecules such as an FXR agonist, an ACC inhibitor, and a GLP1R agonist (cilofexor, firsocostat, and semaglutide) or that include promising molecules such as resmetirom, are currently under investigation. Together with emerging new concepts, it is likely that effective antifibrotic therapy will soon become a reality.

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